REMARKS

In a Final Office Action dated May 16, 2006 the Examiner in charge of the above-noted application rejected Claims 1-12 and 17 under 35 USC 112, first paragraph. Claims 13-16 are withdrawn from consideration for being directed to non-elected subject matter. Applicants' comments are set forth hereinbelow. Accordingly, applicants request reconsideration of the merits of this patent application.

Rejection under 35 U.S.C. §112

Claims 1-12 and 17 stand rejected under 35 USC 112, first paragraph, as failing to comply with the enablement requirement. Specifically, the Examiner asserts on page 3 that the "issue is whether the data from the mouse model would extend the predictability of lowering serum cholesterol in a human patient." The Examiner further asserts that "at the time of filing the technological difficulties in the field of gene therapy (including both safety and efficacy) render the claimed invention unpredictable with regard to lowering serum cholesterol in human patients based on the mouse model." As evidence of unpredictability, the Examiner continues to cite Gotthardt and Schuster (1997) Gene Therapy for Familial Hypercholesterolemia, *Concepts in Gene Therapy*, pgs. 359-386, which allegedly teaches that "major obstacles must be overcome before gene therapy for FH becomes a reality despite the success in animal model." (see page 4-5 of the Office Action). Applicants continue to traverse the rejection.

At the outset, applicants refute the Office's characterization of Gotthardt and Schuster, which was published in 1997 and in-part provides only a selective review of gene therapy for FH up to 1997. In other words, the discussions in Gotthardt relating to *in vivo* gene therapy date back to research articles from 1990 to 1995 (see Section 18.5.5, *In vivo* Gene Therapy, pgs. 370-373). Further, applicants' filing date was July 21, 2000, three years after Gotthardt's review. There was quite a bit of advancement in the gene therapy field between the years 1997 and 2000. Therefore, it is unreasonable for the Office to cite Gotthardt (which speculates upon research results dating back to 1990) for the notion that human gene therapy would not have been enabled in the year 2000, despite the success of gene therapy in animal models.

Indeed, Gotthardt provides that "[T]he problems encountered with the *ex vivo* approach make an *in vivo* approach the method of choice for FH-directed gene therapy." (See pg. 370, ¶ 1, underlining for emphasis). Also, in regard to *in vivo* gene therapy, Gotthardt goes on to say that

> "many different transfer vehicles have been devised, most of which have been shown suitable for liver-directed gene delivery," and that "[R]etroviral vectors have been used in 80% of clinical gene therapy trials, based upon *ex vivo* transduction, with no associated toxicity, despite lack of targeted integration and a high error rate of reverse transcriptase. Among other cells, hepatocytes can efficiently be infected (up to 80% of mouse - and 40% of human hepatocytes) (Pages et al., 1995)." (See pg. 370, ¶¶ 2 and 3).

Gotthardt also indicates that in humans, adenovirus infections have been reported to persist for up to two years (Horowitz, 1990). (See Gotthardt at pg. 371). Thus, even though in 1997 there were obstacles to overcome before human gene therapy became recognized as a viable therapeutic option, it was still viewed as a suitable alternative method of treatment for some patients.

As evidence that human gene therapy was feasible at the time of filing, applicants direct the Examiner's attention to French Anderson's, "The Best of Times, The Worst of Times" *Science*, New Series, Vol. 288, No. 5466, pp. 627-629 (April 28, 2000); enclosed herewith in a Second Supplemental Information Disclosure Statement (IDS). This encouraging article analyzes several studies published around the time of Applicants' filing, where gene therapy treatment was successful. One of these studies is reported by Cavazzana-Calvo *et al.* (2000) *Science* 288, pp. 669-672; enclosed herewith in an IDS. Cavazzana-Calvo *et al.* disclose positive results obtained in human gene therapy clinical trials, where two SCID-X1 patients, ages 11 and 8 months (infants) suffering from inherited x-linked form of severe combined immunodeficiency (SCID-X1) caused by a mutation in the gene encoding the γc subunit (a component of certain cytokine receptors) underwent clinical trials for at least up to 10 months. Cavazzana-Calvo *et al.* took hematopoietic stem cells (which expressed the surface marker CD34 and were capable of differentiating into all types of blood cells) from the infants' bone marrow and incubated the cells *ex vivo* with a retroviral vector

carrying the *γc* cDNA. The transduced stem cells were then transfused back into the SCID-X1 patients. Ten months after receiving transduced stem cells, the numbers of T, B, and natural killer (NK) cells of the immune system were normal, as were a number of measures of immune function (such as specific responses to antigen). The authors assert that clinically, the two patients improved considerably and were able to leave protective isolation in the hospital after 3 months and stayed at home thereafter. That initial data strongly suggested that SCID-X1 could be successfully treated by retroviral-mediated gene therapy.

In addition to the success achieved with gene therapy for the treatment of SCID, other publications in the year 2000 showed amelioration of disease via gene therapy, such as, in the treatment of hemophilia (M.A. Kay et al., (2000) *Nature Genet.* 24, 257; enclosed herewith in an IDS) and in the growth of new blood vessels to treat cardiovascular disease (M. Isner and T. Asahara, (1999) *J. Clin. Invest.* 103, 1231). Furthermore, in 2000 early data demonstrated progress in the development of gene-based vaccines for treating several chronic infectious diseases and some types of cancer. Based on the above, Applicants' maintain that their disclosure at the time of filing enabled lowering serum cholesterol in humans.

Further, the U.S. Patent and Trademark Office has itself issued patents relating to human gene therapy from the period between 1997 to 2001. Examples of some of these patents are recited in Table 1 below.

Table 1

US Patent No.	Title	Priority date
6,844,327	**Gene therapy** approaches to supply apolipoprotein A-I agonists and their use to treat dyslipidemic disorders	September 29, 1997
6,797,703	**Gene therapy** using TGF-Beta	November 1, 2000
6,806,080	Hybrid vectors for **gene therapy**	January 18, 2000
6,815,430	Gene expression base sequences for therapeutic use and drugs for **gene therapy**	March 31, 2000
6,821,753	Replication incompetent herpes viruses for use in **gene therapy**	December 22, 2000
6,825,012	DNA molecules, preparation and use in gene therapy	September 5, 2000
6,846,676	In vivo production and delivery of erythropoietin or insulinotropin for **gene therapy**	November 4, 1994
6,878,549	Packaging systems for human recombinant adenovirus to be used in **gene therapy**	April 24, 1998
6,869,935	**Gene therapy** for proliferative vitreoretinopathy	April 10, 1996
6,800,281	Lentiviral-mediated growth factor **gene therapy** for neurodegenerative diseases	November 8, 2001
6,800,479	Recombinant adenoviruses expressing interleukin-18 protein and **gene therapy** using them	December 11, 2001

The mere fact that these patents issued between 1997-2001 is a testament to the enablement of human gene therapy techniques. Indeed, at the time of filing, gene therapy was viewed as an alternative and suitable treatment for certain patients. Applicants submit that the specification and the relevant art provide sufficient support for the enablement of the claimed invention at the time of filing and reconsideration of this rejection is respectfully requested.

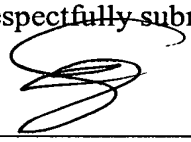
Applicants have made a diligent effort to place the claims in condition for allowance. Also, *no new issues requiring additional searching or further consideration are presented here.* However, should there remain unresolved issues that require adverse action, it is respectfully requested that the Examiner telephone applicants' attorney at the number listed below so that such issues may be resolved as expeditiously as possible. For the reasons stated above this

application is now considered to be in condition for allowance and such action is earnestly solicited.

Fees

A Request for Continuing Examination (RCE) and a Petition for an extension of time accompany this response so that it is deemed timely filed. Please charge these fees to Deposit Account No. 17-0055. No additional fees are believed due; however, should any other extension be due, in this or any subsequent response, please consider this to be a petition for the appropriate extension and a request to charge the extension fee to Deposit Account No. 17-0055.

Respectfully submitted,



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